REMARKS

Claims 14, 17-22, and 35-42 were pending in the instant application. The claims have not been amended. Thus, claims 14, 17-22, and 35-42 will be pending after entry of the instant amendment. Applicants reserve the right to prosecute the claims as originally filed in this or a continuing application.

Objections to Specification

The amendment and substitute sequence listing filed March 5, 2004 (mailed by Applicants on March 5, 2004) are objected to as allegedly introducing new matter by the correction of the sequence of SEQ ID NO:5. The Examiner notes that the sequence of SEQ ID NO: 5 has "two stop codons, one at 1158-1160 and one at 1196-1199" and asserts that "[t]he residues after the first stop codon seem to have proper nucleotide sequences to code for amino acids, therefore it is not clear why the first, not the second stop codon was chosen by Applicants" (emphasis added). (Office Action at page 5, second paragraph of item 5).

Applicants traverse. The Examiner fails to indicate any particular new matter introduced in the prior-filed sequence listing. Applicants indicated the support for SEQ ID NO:5 in the substitute sequence listing in a prior Amendment and Response (mailed March 5, 2004). No matter has been added that goes beyond the scope of the application as filed. Applicants respectfully reassert the arguments set forth in the previous Response filed March 5, 2004 below.

The substitute sequence listing submitted March 5, 2004 merely corrects an error detected in SEQ ID NO:5. The sequence of Figure 10 clearly shows that the RDE-4 amino acid sequence terminates with the C-terminal amino acids YDFTD, directly prior to the first STOP codon, "TGA," at nucleotides 1156-1158. As the Examiner will appreciate, the three codons "TAA", "TAG" and "TGA" are STOP codons that signal the end of the protein-coding message. These codons are not recognized by a tRNA and do not specify an amino acid, but instead signal to the ribosome to ***stop translation*** (see: Molecular Biology of the Cell, fourth edition, 2002,

Eds. B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts and P. Walter; Garland Science, New York, NY, p. 349-350, bridging paragraph). Therefore, the nucleotides 3' terminal to the first STOP codon are non coding. Applicants prior attorneys erroneously included the STOP and residues 3' terminal to the STOP in SEQ ID NO:5. The amino acid sequence of corrected SEQ ID NO:5 is the same sequence disclosed in Figure 10 as originally filed. No new matter has been added.

The Examiner further states that the application fails to comply with the requirements of 37 C.F.R. §§ 1,821-1.825. Accordingly, Applicants submit herewith a Response to Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures to correct an error found in the sequence listing. In particular, the length of SEQ ID NO:5 has been corrected from 407 to 385 amino acids. Applicants submit herewith a new CRF and paper copy of the corrected sequence listing.

Rejection of Claims 14, 17-22, 35-38, 40 and 41 Under 35 USC § 112

Claims 14, 17-22, 35-38, 40 and 41 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner states that "no common element or attributes of the sequences are disclosed, not even the presence of certain domains," and continues that "no functional limitations, other than being a component of an unspecified 'RNAi pathway' have been provided." Examiner continues that "[t]he current situation is a definition of the compound solely b[y] its functional utility, as component of the RNAi pathway, without any definition of the particular amino acid sequence, i.e., structure, claimed."

Applicants traverse. Claims 14, 35 and 36 (and dependent claims 17-22, 37-38, 40 and 41) feature a method of inhibiting the activity of a gene involving the incubation of a dsRNA in the presence of an RNAi pathway component, wherein the RNAi component is an RDE-1 polypeptide or homolog thereof or an RDE-4

polypeptide or homolog. Applicants maintain the position as set forth in the previous Amendment and Response filed March 5, 2004, that the pending claims comply with the written description requirement.

The fundamental factual inquiry in a written description rejection is whether the claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement. MPEP 2163.02. Rather, the inquiry into whether the written description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

Applicants submit that the genera of RDE-1 polypeptides and homologs and the genera of RDE-4 polypeptides and homologs are extensively described in the specification at least in Example 6 and Figure 4. The RDE-1 gene family including known homologs is described and conserved structural features and/or regions are described and depicted in Figure 4. The genus of RDE-4 polypeptides, homologs and fragments is described in the specification at least in Example 11 and Figure 11. Known homologs are described and conserved structural motifs and/or regions are described and depicted in Figure 11. Further, methods of identifying additional RDE-1 or RDE-4 homologs are described at page 10, line 4 through page 12, line 11. Contrary to the Examiner's assertions, functional limitations for the RDE-1 and RDE-4 polypeptides (or homologs thereof) is provided by the inventors at least in Example 6, wherein straightforward assays are described to determine whether a RDE-1 or RDE-4 polypeptide retains the activity of RDE-1 or RDE-4, respectively. Moreover, Example 12 describes assays to determine whether a RDE-1 or RDE-4 domain or fragment retains the activity of RDE-1 or RDE-4, respectively. It is Applicants' opinion that one of skill in the art would recognize the claimed invention based on these teachings in the specification.

In summary, it is Applicants position that, contrary to the Examiner's assertions, the specification is replete with teachings as to the structural and functional characteristics of the claimed genera of polypeptides. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 14, 17, 20-22 and 35 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 14, 17-22 and 35-42 Under 35 U.S.C. § 112

Claims 14, 17-22 and 35 have been rejected under 35 U.S.C. § 112 as allegedly lacking enablement. The Examiner states that the specification, while being enabling for inhibiting activity of a gene by dsRNA *in vitro*, does not reasonably provide enablement for inhibiting activity of a gene by dsRNA *in vivo*. In particular, the Examiner states that the specification does not enable the skilled artisan "to make and use the invention commensurate in scope with the claims," where the claims are broadly drawn to gene targeting by RNA interference in all animals, including mammals. Applicants traverse.

An analysis of an enablement rejection requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). ***The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation***. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

The Examiner concedes that the level of skill in the art is high. The Examiner cites, however, references for the proposition that the art is highly unpredictable, asserts that the amount of guidance provided by the application is insufficient and that the quantity of experimentation necessary to practice the claimed invention is high. The Examiner concludes that the factor of unpredictability in the art "weighs heavily in favor of undue experimentation." Applicants disagree. Applicants submit that the instant specification provides ample guidance to enable one skilled in the art to carry out the claimed invention without undue experimentation.

The Examiner's assertion that the art is highly unpredictable is based largely on certain references cited by the Examiner which describe the PKR response in mammalian systems. As Applicants have previously stated, means of counteracting the PKR response in PKR-proficient mammalian systems were known to skilled artisans at the time the instant application was filed, including peptide antagonists and antisense oligonucleotides (see, e.g., Judware and Petryshyn, Nekhai et al. and WO 98/04717, all of record). Further, Applicants respectfully point out that the *in vivo* methodologies of the instant invention are applicable to a number of *in vivo* systems where the PKR response is not a consideration, for example, invertebrate systems and PKR-deficient systems. Moreover, even in PKR proficient systems, it may not be necessary to eliminate the PKR response in order to benefit from the sequence-specific gene silencing methodologies of the claimed invention. The Examiner will appreciate, for example, that many chemotherapeutic agents have unwanted side effects that do not diminish their therapeutic value. In view of the foregoing and given the high level of skill in the art, it is Applicants' position that the amount of experimentation necessary to carry out the claimed invention in such systems would not be undue.

The Examiner's position that the art is highly unpredictable is based additionally on the proposition that the complete mechanism of RNAi is not yet known. In response, Applicants respectfully submit that the standard for enablement

does not require that the complete mechanism of action of an agent, *e.g.*, the RNAi agent of the instant invention, be known, either in *C. elegans* or in any other system, to enable methods that feature administering such an agent to achieve a desired result.

Finally, additional references are cited by the Examiner for the proposition that administration of the agents of the invention is unpredictable and undue experimentation would be required to practice the invention as claimed. Applicants disagree and respectfully point out that the art and the specification are replete with teachings as to the administration of nucleic acid-based agents (*e.g.*, liposome formulations, direct injection, etc).

The Examiner additionally asserts that the amount of guidance provided by the specification and working examples is insufficient, and that the quantity of experimentation required for a skilled artisan to practice the invention is high. In particular, the Examiner is of the opinion that the skilled artisan would have to perform undue experimentation to identify the mechanism of RNAi gene silencing in a given organism, including, but not limited to, "all of the nucleic acids and proteins necessary for effective and stable gene silencing." In response, Applicants respectfully reiterate their arguments set forth in the previous Amendment and Response filed March 5, 2004.

Applicants submit that the skilled artisan can use RNAi components disclosed in the instant specification, *e.g.*, RDE-1 and/or RDE-4 polypeptides, to prepare RNAi agents according to the instant invention and use these RNAi agents in other systems. Moreover, the specification, having identified important components of the RNAi machinery in *C. elegans*, provides ample teaching to enable the skilled artisan to identify, obtain and/or select similar RNAi components from other systems for use in the claimed methodologies without undue experimentation. The specification, for example, teaches the isolation of homologous genes using two-hybrid screens, hybridization-based assays, complementation-based assays, PCR, and/or database screens, (see, for example, page 10, line 4 through page 12, line 6) all of which are

facilitated by the disclosure of the sequences of the *C. elegans* RNAi components, *e.g.*, RDE-1 and/or RDE-4. Such experimentation is routine in the art.

Importantly, the instant specification goes further to teach that the RNAi components identified in *C. elegans*, *e.g.*, RDE-1 and RDE-4, belong to conserved gene families and, moreover, teaches other family members which share a significant degree of sequence identity and/or structural features with the *C. elegans* genes. These components were identified by the instant inventors using database screens for sequences homologous to the RNAi pathway genes identified by genetic screening. In particular, the specification teaches that RDE-1 shares a significant degree of sequence identity and/or structural features with the Zwille and argonaute proteins from *Arabidopsis*, the Sting and Piwi proteins from *Drosophila*, the eIF2C protein from rabbit, as well as others (see Figure 4B and Example 6). These RDE-1 homologues share significant identity (as depicted, for example, in the sequence alignment of Figure 4B) and are most highly conserved across their Paz and Piwi domains. The specification also teaches proteins having homology to RDE-4, in particular, across the DNA-binding domain (see *e.g.*, Figure 11 and Example 11). Applicants submit that post-filing date references provide evidence that Applicants' teaching that these homologues are functionally related, in addition to their structural relatedness, was borne out. For example, the Fagard *et al.* reference presents data demonstrating that the *Arabidopsis* protein, Argonaute 1 ("AGO1"), is required for gene silencing in plants. The Williams and Rubin reference further demonstrates the activity of AGO1 in mediating RNAi in *Drosophila*. Both the Fagard *et al.* reference and Catalanotto *et al.* reference, teach that the *N. crassa* protein QDE-2, which shares both sequence identity and conserved structural domains with RDE-1 and Argonaute-1 (see *e.g.*, Figure 1 of each reference) controls gene silencing in fungi. The Pal-Bhadra *et al.* reference demonstrates that the *Drosophila* protein, Piwi, is required for gene silencing in flies. Lastly, the Doi *et. al.* reference demonstrates a role for eif2C in promoting RNAi in a mammalian system. Thus, the instant specification is replete

with teachings of RNAi components from other systems for use according to the claimed methodologies which have proved correct.

In summary, the Examiner recognizes that the level of skill in the art is high but concludes that other factors outweigh the high level of skill in the art. ***The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation*** It is Applicants' position that given the high level of skill in the art, engaging in the amount of experimentation necessary to carry out the claimed invention would not be undue. Applicants' position is supported by the post-filing date references discussed above. In the previous Amendment and Response, Applicants cited additional references demonstrating that RNAi has successfully been practiced in several mammalian systems as evidence, including the disclosures of Svoboda *et al.*, Wianny and Zernicka-Goetz and Billy *et al.* references already of record in this case. The Examiner states that these references cannot be enabling because they were published after the filing date of the instant application. Applicants respectfully point out that the references were clearly indicated as post-filing date references and were provided to evidence Applicants' position that, contrary to the Examiner's assertion, ***predictability*** in the art was high.

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 14, 17-22 and 35-42 for lack of enablement under 35 U.S.C. § 112, first paragraph.

Claim Interpretation and Rejections Under 35 USC § 102 and § 103

The Examiner has interpreted claims 14, 35 and 36 as indicated in paragraph 10 of the instant Office Action. Claims 14, 35 and 36 (and dependent claims 21 and 22) have been rejected under § 102(b) as allegedly anticipated by Fire *et al.* (1998 *Nature* 391:806-811) and dependent claim 20 has been rejected under § 103(a) in view of Fire *et al.* and Wheeler *et al.* (U.S. Patent No. 5,976,567) based on the Examiner's claim interpretation. Applicants traverse. Applicants respectfully reassert

the arguments set forth in the previous Amendment and Response filed March 5, 2004 that the claim interpretation is erroneous, and that Fire *et al.* does not anticipate the claimed invention.

Claims 14, 35 and 36 are directed to methods of inhibiting the activity of a gene. The methods comprise the step of ***introducing an RNAi agent into a cell***. The methods further include the limitation that the ***RNAi agent is prepared by incubating a double-stranded RNA in the presence of an RNAi pathway component*** (e.g., RDE-1 polypeptide, RDE-4 polypeptide, homologs of same, *etc.*). Supporting the pending claims, the specification describes an RNAi agent as "***dsRNAs that have been treated with RNAi pathway components*** rendering the treated dsRNA capable of activity in the RNAi pathway and can be used as sequence-specific interfering agents useful for targeted genetic interference" (page 28, lines 23-25). The Examiner errors in interpreting this claim limitation of incubating a dsRNA in the presence of an RNAi pathway component as "incubation of dsRNA with the RNAi pathway components present in the cell into which the dsRNA is introduced." (Office Action at page 16, paragraph 10). While the specification teaches that RNAi agents can be prepared *in vitro* or in cells (page 28, lines 21-31), Applicants respectfully point out that the instant claims require introduction of an ***RNAi agent, not a dsRNA,*** into a cell. The Examiner's interpretation of the limitation is therefore inconsistent with the language of the claims. As stated on the record in Applicants' previous Response filed March 5, 2004, "claim 14 features preparation of RNAi agents *in vitro*" (page 9, first paragraph). Moreover, consistent with this claim interpretation, claims 23-34, featuring preparation of RNAi agents in a cell, have been restricted by the Examiner (and are withdrawn from consideration) as being directed to patentably distinct subject matter (see Office Action dated November 15, 2002). Applicants respectfully submit that the claim interpretation set forth in paragraph 10 of the instant Office Action is inconsistent with the meaning of the claim and with the previous restriction of distinct subject matter.

Applicants further submit that the rejections of claims 14, 21, 22, 35 and 36 under 35 USC § 102(b) and claim 20 under § 103(a) are moot in view of a proper claim interpretation. With respect to the rejections, the Examiner asserts in the Office Action that "Fire et al. teach inhibiting activity of several *C. elegans* genes...by introducing an ***RNAi agent (dsRNA)*** into *C. elegans* (Abstract, Table1)." (Office Action at page 16, paragraph 13). Thus, as stated by the Examiner, Fire *et al.* injected a sequence that was a double-stranded RNA sequence. Fire *et al.* did not inject an RNAi agent as claimed in the instant invention. The double-stranded RNA used by Fire *et al.* was not incubated in the presence of an RNAi pathway component (*e.g.*, an RDE-1 or RDE-4 polypeptide) before introduction into *C. elegans* in order to prepare an RNAi agent according to the instant invention. Thus Fire *et al.* does not introduce an RNAi agent of the instant invention into a cell.

Based on the foregoing arguments, Applicants submit that Fire *et al.* did not use or contemplate the use of an RNAi agent, and thus Fire *et al.* does not anticipate claims 14, 35 and 36. Applicants therefore request reconsideration and withdrawal of the rejection of claims 14, 21, 22, 35 and 36 under 35 USC § 102(b) and claim 20 under § 103(a).

CONCLUSION

In view of the above amendments and remarks, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

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